onset of or ameliorating the effects of an autoimmune disease. Applicants address each of these alleged bases of rejection in the following remarks.

First, the Action alleges that the instant application is not enabling as to any species of *Coxiella* or form of a *Coxiella* species. Without acquiescing to this basis of objection, and solely for the purpose of expediting prosecution of the application, while reserving the right to pursue the original claim scope in a timely filed continuation application, Applicants have amended claims 1 and 15 to specifically recite the species "*Coxiella burnetii,*" instead of "a species of *Coxiella*." In addition, Applicants have amended claims 1 and 15 to include the limitation of "non-infectious." Support for the use of non-infectious *C. burnetii* is provided throughout the specification, including page 6, lines 12-19. The specification recites the use of various forms of *C. burnetii*, including heat-killed and formulin-killed preparations, as well as QVAX and QFA (both available from CSL Limited, Melbourne, Australia), and live, attenuated strains of *C. burnetii*, for example (page 6, lines 12-19). As the Examples clearly enable one of ordinary skill in the art to verify any component of *C. burnetii* as antigenic, Applicants submit that one of ordinary skill in the art would be able to practice the claimed invention without undue experimentation.

Secondly, the Action alleges that the instant specification does not teach how to identify specific *C. burnetii* preparations, or antigenic molecules therefrom, that can be used to treat "any" non-*Coxiella*-related autoimmune disease. The Action bases this allegation primarily on its understanding that an immunogenic heat shock protein (hsp) of *Mycobacterium tuberculosis* causes autoimmune arthritis, and that it has putatively been established in the art that an immunogenic hsp of a mycobacterial species such as *Mycobacterium tuberculosis* is analogous or homologous to the hsp antigen of *C. burnetii*.

Applicants respectfully disagree with this interpretation of the cited references and submit that the correct interpretation does not support the Action's apparent conclusion that an hsp antigen of *C. burnetii* would likely cause autoimmune disease. Rather, Applicants submit that the cited references support the use of an hsp antigen of *C. burnetii* for treatment of autoimmune disease. The relevant passage from the cited reference reads:

> "[t]he 2-kDa polypeptides from C. *burnetii* and *M. leprae* can be aligned for their first 520 amino acids within one to four residues with an overall

> identity of about 55%. The C-terminal 40 residues show considerably more divergence and display homology for only limited small stretches."

Applicants submit that the induction of an immune response is entirely dependent upon the ability of the host to 'recognize' and subsequently mount a reaction to a given antigen. In terms of *antibody production*, immune recognition of a protein is dependent upon tertiary structure and therefore even a single amino acid change (at a critical point) in a given protein, can completely eliminate induction of an immune response to that protein, let alone a 45% alteration in amino acid sequence. In terms of *cell-mediated immunity,* the response is MHC class I or II restricted and it has been suggested that a cell-mediated immune response can be raised against certain T cell epitopes found in hsps of mycobacterial species (van Eden *et al., Nature 331*: 171-173, 1988). It is, however, well established in the literature that in each case, the cell-mediated immune responses were found to be induced only in those animals that were specifically "immunized" with whole organisms in the presence of an immunoadjuvant – almost invariably this was Freund's incomplete adjuvant (mineral oil). It should also be noted that in no case was there any evidence for the induction of arthritis in any of the treated animals described in the present specification nor was there any evidence for the induction of anti-self antibodies in any of the treated animals. Applicants also submit that there is no evidence of any kind that the hsp of *Coxiella* can induce the production of antibodies or a cell-mediated immune response leading to the induction of arthritis.

The Action notes, with regard to the hsp from *Coxiella,* which shares some homology with mycobacterial hsp, that:

> "[t]he successful treatment of an autoimmune disease with such an antigenic component that is homologous or analogous to an antigenic component of *Coxiella,* such as, *Coxiella burnetii,* is not predictable, because the highly conserved prokaryotic hsp molecules show as much as 50% homology or analogy in their amino acid sequence to that of human hsp, a self antigen."

The Action further states:

> "[b]ecause of this antigenic or molecular mimicry, hsp molecules cause autoimmune diseases including arthritis (see...van Eden *et al., Nature 331*: 171-173, 1988) Therefore, induction of antibodies to such a whole antigenic component is unlikely to be therapeutic against any autoimmune disease."

Applicants submit that evidence from van Eden *et al.*, cited in support of this supposition, actually disagrees completely with this interpretation. Thus, the last paragraph of column 1 on page 172 of this reference reads:

> "...[u]nlike immunization with whole mycobacteria, the administration of the 65K antigen emulsified in oil did not induce AA (Table 2) but the immunized rats did show resistance to a subsequent attempt to induce AA by immunization with whole Mt (Mycobacteria) in oil (Table 2)."

Thus, far from *inducing* arthritis in the treated rats, hsp antigen actually *prevented* its induction following challenge with whole mycobacteria. Applicants therefore submit that this basis for the Action's rejection is unsupported by the evidence and, thus, respectfully request that the rejection be withdrawn.

In addition, Applicants hereby submit the enclosed Declaration under 37 C.F.R. § 1.132, which provides further data in support of various fractions of *C. burnetii* being effective in the treatment of IDDM, while other fractions are without such activity. The data provided in the Declaration further establish that the instant specification fully enables one of ordinary skill in the art to practice the invention without undue experimentation. For example, the Declaration provides clear evidence that the residue (CMR) remaining after delipidation of whole *C. burnetii* was very effective, in a highly statistically significant manner at preventing the onset or development of IDDM in the NOD mouse, while the components of the extracted lipidic material (CME) were without effect. In addition, the Declaration demonstrates that a DMSO extract of whole cell *C. burnetii* was also highly effective at inhibiting the onset of IDDM in NOD mice, preventing the onset of diabetes by 100%. The LPS fraction of *C. burnetii* (prepared as described by Schramek and Galanos, *Wcta Virol. 25*: 230-234, 1981) was also isolated and tested for its ability to inhibit the development of IDDM in the NOD mouse and found to be inactive. The preparation of the CMR and CME fractions has been described in the literature (Williams *et al., Infection and Immunity, 51*: 851-858, 1986). The preparation of the LPS fraction of *C. burnetii* has also been described in the literature. The preparation of the DMSO extract is provided in the accompanying Declaration.

The Action specifically alleges that the specification does not provide evidentiary support showing that a membrane/cell wall preparation of the invention does prevent, inhibit,

ameliorate or delay onset of any non-coxiella-induced autoimmune disease, including IDDM. Applicants respectfully submit that such additional evidentiary support is not necessary based upon the teachings and Examples provided by the instant specification. Nevertheless, Applicants provide further evidence in the accompanying Declaration. The preparation of cell wall material from *C. burnetii* has been previously described (Amano, *et al., J. Bacterial. 160*: 982-988, 1984). Applicants submit that evidence in the accompanying Declaration demonstrates that a cell wall fraction of *C. burnetii* prepared using this procedure had a protective effect against the development of IDDM in the well-accepted NOD mouse model. Thus, Applicants submit that the invention is fully enabled, and one of ordinary skill in the art would be apprised to the methods of identifying and reproducibly producing the claimed components of *C. burnetii*.

Applicants submit that all pending claims are adequately enabled, particularly in light of the clarification and supporting information provided in the accompanying Declaration. Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

Rejection under 35 U.S.C. § 103(a), Obviousness

Claims 1, 2, 15, 16, 20, and 21 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zhang *et al.* or Gajdosova *et al.*, each in view of Levy *et al.* or Rouse *et al.* The Action alleges that Zhang *et al.* teaches a composition comprising a purified antigenic outer membrane component of *Coxiella burnetii* and its potential use as a subunit vaccine against Q fever, as well as the use of a suspension of killed phase I whole cell vaccines of *C. burnetii* in humans and animals. In addition, the Action alleges that Gajdosova *et al.* teach a composition comprising phase I *C. burnetii* whole cells or Cb I and/or outer membrane components of *C. burnetii* contained in a pharmaceutically accepted carrier. The Action concedes that neither Zhang *et al.* nor Gajdosova *et al.* expressly teach a composition for preventing, inhibiting, or ameliorating an autoimmune disease in a mammal. Rather, the Action alleges that Levy *et al.* teach an association between Q fever and autoimmune disorders through evidence of autoimmune antibodies, while Roue *et al.* teach that acute Q fever is associated with autoimmune disorders and development of autoimmune serological markers.

Applicants respectfully submit that the cited prior art, either alone or in combination, clearly fails to teach or suggest the use of components of *C. burnetii* for preventing,

inhibiting, delaying onset of or ameliorating the effects of autoimmune disease. Applicants submit that the invention is not obvious over the cited prior art, since Zhang *et al.* and Gajdosova *et al.* do not teach a composition for preventing, inhibiting, or ameliorating an autoimmune disease in a mammal, and neither Levy *et al.* or Roue *et al.* remedy this deficiency. More specifically, Applicants maintain that neither Levy *et al.* nor Roue *et al.* teach or suggest that compositions of the invention or compositions disclosed in Zhang *et al.* or Gajdosova *et al.* would be effective in preventing or treating the effects of autoimmune diseases. Rather, the findings of Levy *et al.* and Roue *et al.* allegedly suggesting an association between Q fever and autoimmune disease do not appear particularly relevant as to the claims of the instant application. Applicants submit that autoimmune responses can and do occur following bacterial or viral infection or vaccination, and it is not strictly limited to any specific virus or bacteria or family thereof. Thus, the potential for production of autoimmune phenomena following any infection is real and well noted in the medical literature. Indeed, Applicants note that any time an infection occurs in which antibodies are raised against the infectious agent, there is a very high likelihood that anti-idotypic antibodies will be formed. In this case, the anti-idiotypes are, in the strictest sense, autoimmune antibodies since they cross-react with molecules that are "self". Specifically, the anti-idiotypes are raised against the antibodies that are produced in response to the invading pathogen. This phenomenon is extremely well known in the literature. This reaction does not, however, usually lead to clinical signs of disease. Thus, the potential for production of autoimmune phenomena following any infection is real and well noted in the medical literature.

However, Applicants note that many infections can also give rise to tissue cross-reacting antibodies which may cause clinical disease signs. Applicants submit there are numerous examples of autoimmune diseases induced by viral infection. This phenomenon is *not* unique to *Coxiella* or to mycobacteria or even to bacteria. One well known example of an autoimmune disease induced by a virus infection is acute disseminated encephalomyelitis (ADE) which can occur days to weeks following viral illness or vaccination (this is well documented in Alvord, EC Jr., Disseminated encephalomyelitis: its variations in form and their relationships to other diseases of the nervous system. In: Vinken, PJ, Bruyn, GW, Klawans HL Eds. *Handbook of clinical neurology.* Vol 47, series 3. Amsterdam: elsevier Science Publishers, 1985: 467-502). Many other publications give insight into this phenomenon (see for example Straub *et al.,* Early

high-dose intravenous methylprednisolone in acute disseminated encephalomyelitis: A successful recovery, *Neurology 49*: 1145-1147, 1997; Kanter *et al.,* Plasmapheresis in fulminant acute disseminated encephalomyelitis, *Neurology 45*: 824-827,1995; Koenig *et al.,* Post-infectious encephalomyelitis after successful treatment of herpes simplex encephalitis with adenine arabinoside, *New England Journal of Medicine 300*: 1089-1093, 1979). Rabinowitz *et al.,* (Endogenous myelin basic protein-serum factors (MBP-SFS) and anti-MBP antibodies in a patient with post-herpes simplex virus acute disseminated encephalomyelitis, *J Neurol Sci* 1983 *Aug-Sep;60(3):* 393-400) have described:

> "[t]he measurement of myelin basic protein serum factors (MBP-SFs) and anti-MBP antibodies in specimens from a patient with post-herpes simplex acute disseminated encephalomyelitis (ADE) ..."

Others have made similar findings, for example, see Pohl-Koppe *et al.,* (Myelin basic protein reactive Th2 cells are found in acute disseminated encephalomyelitis), *J. Neuroimmunol. 91*: 19-27, 1998). Other infection induced autoimmune diseases are also known. For example, encephalo-myelo-radiculoneuropathy can occur following viral infection (Nomura *et al.*, Two cases of encephalo-myelo-radiculoneuropathy, triggered by herpes simplex virus type-1 infection, *Rinsho Shinkeigaku, 37*: 621-625, 1997). Based on these previous findings, Applicants respectfully submit that the findings of neither Levy *et al.* nor Roue *et al.* teach or suggest that a composition of the invention would be useful in preventing or treating autoimmune disease. Rather, such references actually teach away from the surprising results obtained by the present invention, since they suggest that the compositions of the invention might actually promote autoimmune disease.

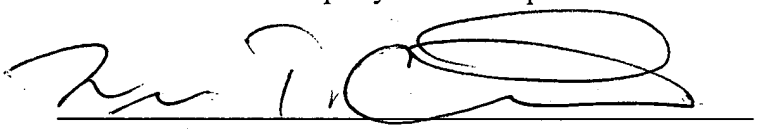
In conclusion, Applicants respectfully submit that the presently pending claims are non-obvious based upon the cited references and request that the Examiner withdraw the rejection under 35 U.S.C. § 103(a).

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

Applicants respectfully submit that all of the claims remaining in the application are now allowable. However, should any outstanding issues remain, the Examiner is encouraged to contact the undersigned at 206-622-4900. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Seed Intellectual Property Law Group PLLC



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WTC:rap

Enclosures:
Postcard
Check
Petition for an Extension of Time
Declaration of Dr. Cowden under 37 C.F.R. § 1.132

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please amend claims 1 and 15 as follows:

1. (Twice Amended) A method for preventing, inhibiting, delaying onset of or ameliorating the effects of an autoimmune disease in a mammal, said method comprising administering to said mammal an autoimmune-preventing effective amount of [a species of] non-infectious *Coxiella burnetii* or one or more antigenic components therefrom.

15. (Twice Amended) A therapeutic composition for use in preventing, inhibiting, delaying onset of or ameliorating the effects of an autoimmune disease in a mammal, said composition comprising [a species of] non-infectious *Coxiella burnetii* or one or more antigenic components therefrom and one or more pharmaceutically acceptable carriers and/or diluents.

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